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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,305	CHOI ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29 and 37-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 August 2009* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 7/28/2009, in which claims 30, 31, 35 and 36 were canceled, claim 29 was amended, and claims 37-39 were newly added. Claims 29 and 37-39 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group II and ferritin H chain (BC 012314) with traverse in the reply filed on 1/19/2009.

Claims 29 and 37-39 are under consideration.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application 10-2004-0004308 filed in The Republic of Korea on 1/20/2004. Where applicant has complied with PCT Rule 17, the International Bureau will forward a copy of the certified priority document to each Designated Office that has requested such document with an indication that the priority document was submitted in compliance with the rule and the date the document was received by the International Bureau. In the instant case, inspection of the file for PCT/KR05/00188 reveals that Applicant did not comply with PCT Rule 17. The International Bureau has not forwarded a copy of the certified priority document. If the International Bureau

is unable to forward a copy of the certified priority document to the U.S. Patent and Trademark Office because applicant failed to comply with PCT Rule 17(a)-(b), then applicant will have to provide a certified copy of the priority document (or have the priority document furnished in accordance with 37 CFR 1.55(d)) during the national stage to fulfill the requirement of 37 CFR 1.55(a)(2). In the instant case, applicant will have to provide a certified copy of the priority document.

Response to Arguments - Priority

At page 11, the response notes that Applicants have submitted a verified statement on translation. Applicants indicate that a certified copy of the Korean priority document will be submitted in due course.

The verified statement on translation was received on 7/28/2009. The certified copy of the Korean priority document has not yet bee received.

Drawings

The drawings are objected to because the description of FIG. 3a - FIG. 3f refers to colors in the drawings, where the cluster frequency over 80 was marked red, the frequency of 50-79 was marked yellow, the frequency of 30-49 was marked green, and the frequency under 29 was marked blue (page 21, lines 10-15). The color referred to in the brief description of the drawings cannot be seen in the black and white drawings. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the

immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. Alternatively, the brief description of the drawing can be amended such that it does not refer to colors that cannot be seen. The objection to the drawings will not be held in abeyance.

It is noted that color photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

Response to Arguments - Drawings

Applicant's arguments filed 7/28/2009 have been fully considered but they are not persuasive. At page 11, the response asserts that the objection to the drawings has been overcome by color photomicrographs of Figures 3A-3F, which were mailed to the USPTO.

This argument is not persuasive. It is noted that color photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. In the instant case, Applicants filed a petition on 8/3/2009 to accept color photographs. The petition was denied for the reasons set forth in the Office letter mailed 10/21/2009. Therefore the objection to the drawings is maintained for the reasons set forth above.

Specification

The amendment filed 7/28/2009 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the amino acid sequence of SEQ ID NO: 49.

At page 12, the response asserts that Ferritin H chain (BC12314) is described in the specification as originally filed. Further, the response asserts that an ordinary person in the art can easily search protein sequence and nucleotide sequence from BC12314 by using the NCBI website. The response notes that this is the first time the sequence is presented, but it should not be considered to be new matter because the sequence was available to the public and the specification as originally filed stated where the sequence information could have been found.

The specification as originally filed fails to provide literal or inherent support for the sequence of SEQ ID NO: 49. The original claims present on the filing date are accepted as a clear intent to incorporate the nucleic acid sequence of GenBank Accession No. BC12314. The originally filed claims were drawn to treating cells with an effective amount of a ferritin H chain (BC012314) gene. GenBank Accession No. BC012314 (GI: 15126787, publicly available August 2001) describes a cDNA clone of the *Mus musculus*, ferritin heavy chain gene. The entry is directed to the nucleic acid sequence, and the originally filed claims were directed to the administration of a gene (i.e., nucleic acid). The originally filed application did not convey intent to incorporate the amino acid sequence described as the coding sequence of ferritin heavy chain with the GenBank Accession No. BC12314 features description.

Applicant is required to cancel the new matter in the reply to this Office Action.

Response to Arguments – Specification

The previous objections to the specification have been withdrawn in view of Applicant's amendment to the specification in the reply filed 7/28/2009.

Double Patenting (Warning)

Applicant is advised that should claim 37 be found allowable, claim 39 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other

as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 39 depends from claim 37 but does not further limit claim 37. Thus, both claims are identical in scope.

Claim Objections

Claim 39 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 39 depends from claim 37, and both claims depend from claim 29. Claim 37 recites, "wherein the nucleotide of the ferritin H chain is represented by SEQ ID NO:50." Claim 39, recites, "The method as set forth in claim 37, wherein the nucleotide of the ferritin H chain is represented by SEQ ID NO:50." Claim 39 does not add any further limitations to the method of claim 37. Thus, claim 39 fails to further limit claim 37.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection, necessitated by the addition of new claims 37 and 39 in the reply filed 7/28/2009.

Claim 37 recites the limitation "the nucleotide" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 37 depends from claim 29,

which is drawn to treating premature natural killer cells with an effective amount of ferritin H chain (BC012314) represented by SEQ ID NO: 49. SEQ ID NO: 49 is a protein sequence of 182 amino acids. Claim 29 does not recite a "nucleotide" or "nucleotide sequence" or "gene." Thus, the claims lack antecedent basis for a nucleotide or nucleotide sequence, and it is unclear whether the nucleotide sequence refers to an element that was previously presented in the claims. One of ordinary skill in the art does not know what applicant is attempting to further limit with respect to the limitation of "the nucleotide of the ferritin H chain is represented by SEQ ID NO: 50."

Claim 39 recites the limitation "the nucleotide" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 39 depends from claim 37, which depends from claim 29, which is drawn to treating premature natural killer cells with an effective amount of ferritin H chain (BC012314) represented by SEQ ID NO: 49. SEQ ID NO: 49 is a protein sequence of 182 amino acids. Claim 29 does not recite a "nucleotide" or "nucleotide sequence" or "gene." Although claim 37 recited "the nucleotide" it does not clarify the relationship of the sequence of SEQ ID NO: 50 to the claimed method, because it is identical in wording to claim 39. Thus, the claims lack proper antecedent basis for a nucleotide or nucleotide sequence, and it is unclear whether the nucleotide sequence refers to an element that was previously presented in the claims. One of ordinary skill in the art does not know what applicant is attempting to further limit with respect to the limitation of "the nucleotide of the ferritin H chain is represented by SEQ ID NO: 50."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29 and 37-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

In the reply filed 7/28/2009, claim 29 was amended to require the step of "treating premature natural killer cells with an effective amount of ferritin H chain (BC012314) represented by SEQ ID NO: 49." New claims 37 and 39 limit the method of claim 29 to the method, "wherein the nucleotide of the ferritin H chain is represented by SEQ ID NO: 50." New claim 38 is drawn to a method comprising the step of "treating to premature natural killer cells, an effective amount of ferritin H chain (BC012314) represented by SEQ ID NO: 49."

The prior version of claim 29 was directed to the step of treating premature natural killer cells with an effective amount of ferritin H chain (BC012314) gene. The recitation of GenBank Accession No. BC012314 was interpreted as intent to incorporate the nucleotide sequence of BC012314. GenBank Accession No. BC012314 (GI: 15126787, publicly available August 2001) is a nucleotide sequence record that describes a cDNA clone of the *Mus musculus*, ferritin heavy chain gene. The originally filed disclosure is directed only to the administration of genes to cells (e.g., page 1, lines 8-12; page 3, lines 18-22; page 4, lines 21-24; pages 7-9; paragraph bridging pages 11-12). The originally filed disclosure does not provide support for the treatment of cells with a protein encoded by the nucleotide sequence of BC012314.

Furthermore, the claims are drawn to the use of a protein "represented by" SEQ ID NO: 49 or a nucleotide sequence "represented by" SEQ ID NO: 50. The term "represented by SEQ ID NO: 49" is reasonably interpreted as indicating the sequence of SEQ ID NO: 49 is an example of a sequence of ferritin H chain protein. The claim language is broad and does not limit the sequence of the administered protein to the sequence of SEQ ID NO: 49. The term "represented by SEQ ID NO: 50" is reasonably interpreted as indicating the sequence of SEQ ID NO: 50 is an example of a sequence of ferritin H chain protein. The claims are broader than the originally filed disclosure in that they encompass protein sequences of ferritin H chain, and they encompass nucleotide sequences other than the sequence of SEQ ID NO: 50. This broadening results in the introduction of new matter into the claims.

At page 11, the response asserts that the amendment of the claims to refer to SEQ ID NO: 49 and SEQ ID NO: 50 does not introduce new matter even though the sequences are presented for the first time in the amendment filed 7/28/2009. The response asserts that the inclusion of the sequences should not be considered new matter because the sequence was available to the public and the specification as originally filed stated where the sequence information could have been found.

This argument is not found persuasive, because the originally filed application did not convey intent to incorporate the amino acid sequence described as the coding sequence of ferritin heavy chain with the GenBank Accession No. BC12314 features description. Further, the originally filed specification does not provide support for nucleotide sequences "represented by" the nucleotide sequence of SEQ ID NO: 50 or Accession No. BC012314. The originally filed

specification only provides support for the use of the nucleotide sequence of SEQ ID NO: 50 in the claimed methods.

The original specification, drawings and claims were thoroughly reviewed and no support could be found for the amendment. Accordingly, the amendment is a departure from the specification and claims as originally filed, and the recitation of ferritin H chain (BC012314) gene in the originally filed claims and specification does not provide support for the full scope of the claims as amended.

Claims 29 and 37-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was made in the Office action mailed 4/28/2009 but has been rewritten to address the amendments to the claims in the reply filed 7/28/2009.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claims 29, 37 and 39 are drawn to a method of differentiating a stem cell into a mature natural killer cell. The claims are drawn to the step of "treating premature natural killer cells with an effective amount of ferritin H chain (BC012314)

represented by SEQ ID NO: 49." Claims 37 and 39 recite "wherein the nucleotide of the ferritin H chain is represented by SEQ ID NO: 50." However, it is unclear how these claims further limit the method of claim 29, because claim 29 does not recite a nucleotide. The sequence of SEQ ID NO: 49 is an amino acid sequence. The nature of the invention is complex in that the preamble requires the differentiation of a stem cell to a natural killer cell, yet the method steps are drawn to contacting a premature natural killer cell with a ferritin H chain protein. One would not be able to use the method to differentiate a stem cell when a stem cell is not provided and treated by the method. Furthermore, the nature of the invention is complex in that the ferritin H chain protein "represented by" SEQ ID NO: 49 must be capable of differentiating a premature natural killer cell to a natural killer cell.

Claim 38 is drawn to a method of differentiating a premature natural killer cell into a mature natural killer cell, comprising treating premature natural killer cells with an effective amount of ferritin H chain (BC012314) "represented by" SEQ ID NO: 49. The nature of the invention is complex in that the ferritin H chain protein represented by" SEQ ID NO: 49 must be capable of differentiating a premature natural killer cell to a mature natural killer cell.

Breadth of the claims: Claims 29 and 37-39 read on the administration of the ferritin H chain (BC012314) gene to cells *in vitro* or *in vivo*. The claims broadly encompass the administration of a protein of any sequence "represented by" SEQ ID NO: 49. The term "represented by" is reasonably interpreted as indicating the sequence of SEQ ID NO: 49 is an example of a sequence of ferritin H chain. The claim language is broad and does not limit the sequence of the administered protein to the sequence of SEQ ID NO: 49.

Guidance of the specification: The specification asserts that ferritin H gene (BC012314)

is a differentiation regulating agent for natural killer cells (e.g., page 6). The specification asserts that the gene can be used to regulate the differentiation of pNK cells to mNK cells and to treat cancers (e.g., page 10, line 21 to page 12, line 23). The specification provides general guidance with regard to the administration of pharmaceutical formulations and envisions the use of oral or parenteral administration of the gene (e.g., page 12, line 25 to page 14, line 8).

The specification teaches the isolation of hematopoietic stem cells (HSCs) from the tibia and femur of a C57BL/6 mouse (e.g., paragraph bridging pages 22-23). The cells had over 96% purity (e.g., page 23, lines 9-13). The specification teaches that the mouse HSCs can be differentiated *in vitro* to pNK cells and further differentiated *in vitro* to mNK cells (e.g., page 23, line 15 to page 24, line 24). To differentiate the HSCs to pNK cells, the HSCs were cultured in RPMI complete medium supplemented with mouse SCF, mouse Flt3L, mouse IL-7, indomethacin, gentamycin and 10% fetal bovine serum (e.g., paragraph bridging pages 23-24). After 6 days in culture, the cells had differentiated to form pNK cells, which are CD122+ cells. The cells had over 92% purity (e.g., paragraph bridging pages 23-24). To induce the differentiation of pNK cells to mNK cells, the CD122+ cells were incubated with OP9 stromal cells in the presence of mouse IL-15. On day 12, NK1.1+ cells were obtained (e.g., page 24, lines 11-24). The specification teaches the analysis of gene expression from HSCs, pNK and mNK cells using Serial Analysis of Gene Expression (SAGE) (e.g., page 26, line 9 to page 39, line 1). The specification discloses 30 different genes that were identified by the SAGE procedure as specifically expressed at the pNK cell stage. These genes are recited in Table 4 at pages 35-37 of the specification. Ferritin H chain (BC012314) is included in this table at row 2. Further, the expression of Ferritin H chain was studied by RT-PCR using the primers disclosed

as SEQ ID NOs: 27 and 28 (e.g., page 39, line 1 to page 41, line 18). By RT-PCR analysis ferritin H chain (BC012314) expression was detected in HSC, pNK, mNK (-OP9) and mNK (+OP9) (Figure 4B).

Existence of working examples: No working examples of the claimed method are provided. No working examples are provided that demonstrate the ability of ferritin H chain protein to induce pNK cells differentiation to form mNK cells in the absence of other factors (e.g., the cytokines used in the disclosed culture conditions or alteration in the expression of other genes that are disclosed as being involved in the differentiation process).

Predictability and State of the art: The state of the art with regard to involvement of ferritin H gene in controlling the differentiation of pNK cells to mNK cells was underdeveloped at the time the invention was made. The prior art teaches that ferritin is a ubiquitous and highly conserved iron-binding protein composed of two subunits termed H and L (Torti et al. The Journal of Biological Chemistry, Vol. 263, No. 25, pages 12638-12644, 1988; e.g., page 12638, right column, 3rd full paragraph). Torti et al teach that ferritin functions in the storage and delivery of iron for intracellular use, and it functions in detoxification of elemental iron, which is toxic in a non-complexed form (e.g., page 12638, right column, 3rd full paragraph). Thus the prior art does not provide clear support for a role for ferritin H chain (BC012314) in natural killer cell differentiation, and the specification does not provide evidence that increased expression of ferritin H chain (BC012314) by delivering a protein or nucleic acid molecule comprising the sequence of BC012314 to pNK cells will be sufficient to induce differentiation to mNK cells. Accordingly, the effects of exogenous BC012314 expression in pNK cells would have been unpredictable.

If claims 37 and 39 are interpreted as requiring administration of a nucleic acid molecule, it is noted that an analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature, Vol. 389, pages 239-242, 1997; e.g. page 239, paragraph 1) and Palù et al (J. Biotechnol. Vol. 68, pages 1-13, 1999; e.g. Abstract) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al (1997) indicate that most approaches suffer from poor efficiency and transient expression of the gene (e.g. page 239, right column, paragraph 2). Likewise, Luo et al (Nature Biotechnology, Vol. 18, pages 33-37, 2000) indicate that non-viral synthetic delivery systems are very inefficient (e.g. Abstract; page 33, left column, paragraphs 1 and 2). Around the time the invention was made, the art indicates that gene therapy methods still suffer from inefficient gene transfer (Verma and Weitzman, Gene Therapy: Twenty-first century medicine. Annual Review of Biochemistry, Vol. 74, pages 711-738, 2005; e.g. page712, last paragraph). Regarding viral methods for gene delivery *in vivo*, Verma et al (1997), indicate that lentiviral, adenoviral and AAV vectors are capable of delivery genes, but there is a possibility for insertional mutagenesis or toxicity due to an inflammatory response (e.g. Table 2). The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect. Gene therapy is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique (e.g. Verma et al, p. 242, col. 2-3; Palù et al, pp.

10-11; Luo et al, p. 33, col. 1, 1st paragraph; Verma and Weitzman, page 732, 2nd full paragraph).

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use the claimed methods. First, one would need to provide proteins "represented by" the sequence of SEQ ID NO: 49 that are ferritin H chain proteins. Second, one would be required to perform a large amount of trial and error experimentation to use the ferritin H chain protein to induce the differentiation of pNK cells to mNK cells. The prior art does not teach a role for ferritin H chain in the differentiation of NK cells, the specification does not provide evidence that ferritin H chain protein alone is sufficient to induce NK cell differentiation, and the specification teaches detectable expression of ferritin H chain in HSCs, pNK cells, and mNK cells by RT-PCR. Third, if the claims are directed to the administration of a nucleic acid molecule, one would have to determine how to deliver the ferritin H chain (BC012314) nucleic acid molecule to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some differentiation of stem cells to natural killer cells or the differentiation of premature natural killer cells to mature natural killer cells. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 29 and 37-39 are not considered to be enabled by the instant specification.

Response to Amendment – Declaration of Dr. Inpyo Choi

The declaration under 37 CFR 1.132 filed 7/28/2009 is insufficient to overcome the rejection of claims 29 and 37-39 based upon insufficiency of disclosure under 35 U.S.C. 112, first paragraph, as set forth above. The declaration has not been signed. Even if the declaration were signed, it would not be sufficient, because the evidence presented is not commensurate in scope with the claims.

The claimed invention requires the administration of a ferritin H chain protein represented by SEQ ID NO: 49 to premature natural killer cells to differentiate the cells to mature natural killer cells. Thus, administration of the ferritin H chain protein must be sufficient to induce differentiation of a premature natural killer cell (pNK) to a mature natural killer cell (mNK).

At paragraph 6, the declaration states that to confirm whether pNK-specific expression of Ferritin H was required for the differentiation into mNK, hematopoietic stem cells (HSCs) were cultured for 6 days, and then treated with IL-5 and Ferritin H in the absence of OP9 stromal cells, followed by measuring the percentage of NK cells. At paragraph 7, it is stated that HSCs were treated with IL-15 and Ferritin H together, or IL-15 only (presumably reference to IL-5 in paragraph 6 is a typographical error). At paragraph 7, it is disclosed that the use of IL-15 and Ferritin H together, increased the percentage of NK cells as compared to treatment with IL-15 alone. The results also appear to be presented in a figure attached as Exhibit B; however, this exhibit is not specifically referred to in the declaration.

The evidence is not commensurate in scope with the claimed invention. The declaration does not demonstrate that Ferritin H chain alone is sufficient to induce NK cell differentiation from a pNK cell to an mNK cell. The evidence presented demonstrates that the combination of IL-15 and Ferritin H chain is better than IL-15 alone to induce differentiation of NK cells from HSCs. The claims are not drawn to the differentiation of HSC to NK cells, rather the claims require the differentiation of pNK cells to mNK cells. Also, the claims are not directed to the combination of IL-15 and Ferritin H chain.

The evidence presented is not sufficient to overcome the *prima facie* case of non-enablement.

Response to Arguments - 35 USC § 112

The rejection of claims 30, 31, 35 and 36 under 35 U.S.C. 112, first paragraph, is moot in view of Applicant's cancellation of the claims in the reply filed 7/28/2009.

With respect to the rejection of claims 29 and 37-39 under 35 U.S.C. 112, first paragraph, Applicant's arguments filed 7/28/2009 have been fully considered but they are not persuasive.

At page 12, Applicant notes that a new sequence listing has bee provided, in which the amino acid sequence of Ferritin H chain is indicated as SEQ ID NO: 49 and the nucleotide sequence is indicated as SEQ ID NO: 50. Applicant asserts that even though the sequences are presented for the first time, they should not be considered new matter.

Even if the sequences are not new matter, they are not sufficient to overcome the rejection of record, because the sequences alone do not demonstrate that one could use the invention as claimed.

At pages 12-13, the response directs the Examiner's attention to the Declaration of Dr. Inpyo Choi. The response points to Exhibit B, which is asserted to show the effects of Ferritin H chain on NK cells. The response notes that Exhibit B shows that when HSC were treated with IL-15 and Ferritin H together, as compared to IL-15 alone, more NK cells were produced. The response asserts that this demonstrates that Ferritin H plays an important role in the differentiation from pNK cells into mNK cells, and the search for genes regulating NK cell differentiation was correctly carried out according to the presently claimed invention.

The evidence is not commensurate in scope with the claimed invention. The declaration does not demonstrate that Ferritin H chain alone is sufficient to induce NK cell differentiation from a pNK cell to an mNK cell. The evidence presented demonstrates that the combination of IL-15 and Ferritin H chain is better than IL-15 alone to induce differentiation of NK cells from HSCs. The claims are not drawn to the differentiation of HSC to NK cells, rather the claims require the differentiation of pNK cells to mNK cells. Also, the claims are not directed to the combination of IL-15 and Ferritin H chain.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston
Examiner
Art Unit 1636

/JD/

/ Christopher S. F. Low /
Supervisory Patent Examiner, Art Unit 1636